A Phase 1b, Open-label Study in Patients with Cold Urticaria (ColdU) Using THB001, an Orally Available, Potent and Highly Selective Small Molecule Inhibitor of Wild Type KIT Receptor Tyrosine Kinase

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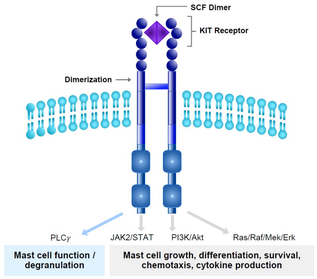
BACKGROUND

THB001 is a highly selective inhibitor of the KIT receptor tyrosine kinase intended for the treatment of mast cell driven diseases[1]. THB001 binds to the tyrosine kinase domain of KIT, preventing autophosphorylation and subsequent dimerization of the receptor, blocking downstream signaling.

Inhibition of Kinases by THB001 in Ba/F3 Assays

Target Kinase	IC_{50} (μM)	Fold Potency vs. KIT
KIT	0.02	-
CSF1R (FMS)	0.95	48
PDGFR-β	2.11	106
PDGFR-α	3.95	198
FLT3	>10.7	>535



Inhibition of KIT results in depletion of mast cells which are considered to be the major effector cell in most forms of urticaria.

Chronic inducible urticarias (CIndUs) are a subgroup of chronic urticaria characterized by the recurrence of itchy wheals and/or angioedema for longer than 6 weeks.

Symptoms in CIndU patients develop only and reproducibly in response to the trigger stimulus that is specific for their condition.

In patients with cold urticaria (ColdU) pruritic wheals appear after cooling and rewarming of the skin. Symptoms typically occur within minutes after skin contact with a cold stimulus and persist for hours. Severe cases may show systemic involvement including anaphylaxis[2,3].

Patients with ColdU experience a negative impact on quality of life – including limitations on recreational activities, ability to work, ability to go outside or to places where temperature is not controlled.

METHODS

Study Design

Open-label, non-randomized, sequential dose escalation study conducted at 2 centers in Europe (Netherlands & Germany)

Population

- Men and women between the ages of 18-75 diagnosed with Cold Urticaria for a minimum of 3 months and refractory to antihistamine treatment
- Positive cold stimulation test at Screening and Baseline
- Otherwise healthy based on a medical evaluation including medical history, physical examination, vital signs, laboratory tests and ECG

Dosing

- 100 mg capsules taken twice daily (BID) in the morning and evening (approximately every 12 hours) for 12 weeks
- Three planned dose levels for a total daily dose of 400 mg, 600 mg, 800 mg

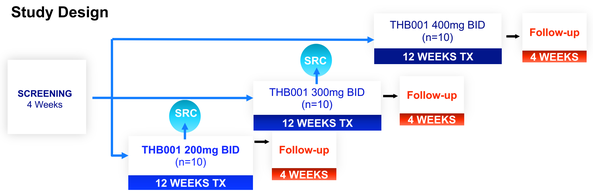
Safety Assessments

- Adverse Event (AE) monitoring
- Clinical laboratory evaluations: chemistry, hematology, and coagulation
- 12-lead ECG, vital signs, physical examinations

Pharmacokinetic, Pharmacodynamic and Efficacy Assessments

- Serum THB001 concentration
- Serum Tryptase
- Critical Temperature Threshold (CTT) as measured with TempTest®

Study Design



RESULTS

Figure 1. Demographics and Baseline Characteristics

Variable		200 mg BID (N=5)
Sex, n (%)		
	Female	5 (100%)
Age (years)		
	Mean (min, max)	29.6 (19-45)
Race, n (%)		
	White	4 (80%)
	Asian	1 (20%)
BMI (kg/m2)		
	Mean (min, max)	22.8 (20-26)
Cold Urticaria Duration (years)		
	Mean (min, max)	4.8 (0.8-10.3)
Serum Tryptase (μg/L)		
	Mean (min, max)	3.74 (1.3 – 6.2)
Critical Temperature Threshold (°C)		
	Mean (min, max)	18.8 (13 - 24)

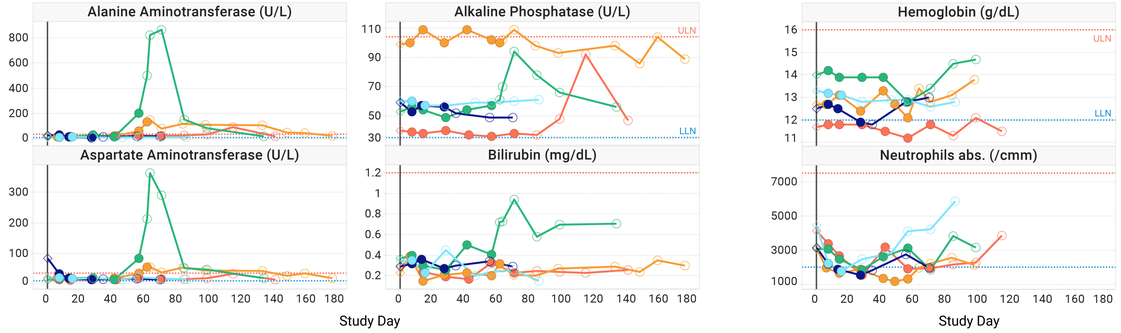
Figure 2. Treatment-Emergent Adverse Events Reported in >=2 Participants

MedDRA Preferred Term	200 mg BID (N=5) Mild N (%)	Moderate N (%)	Overall N (%)
Hair colour changes	5 (100%)		5 (100%)
Abdominal pain	3 (60%)		3 (60%)
Cold urticaria	3 (60%)		3 (60%)
Drug-induced liver injury (DILI)		2 (40%)	2 (40%)
Gastrooesophageal reflux disease	2 (40%)		2 (40%)
Headache	2 (40%)		2 (40%)
Nausea	2 (40%)		2 (40%)
Neutrophil count decreased	2 (40%)		2 (40%)
White blood cell count decreased	2 (40%)		2 (40%)

- The first participant completed 12 weeks of treatment.
- Two participants discontinued at week 8 due to AEs of drug-induced liver injury rated as moderate in severity. AEs resolved at weeks 17 and 25.
- The 2 remaining participants were discontinued from study drug at weeks 3 and 4 and were followed for safety.
- No SAEs were reported.
- No clinically significant findings on ECG or vital signs
- No issues with study drug compliance
- Cold urticaria relapse/exacerbation reported after discontinuing study drug

Figure 3. Liver Panel by Participant

Figure 4. Hematology by Participant



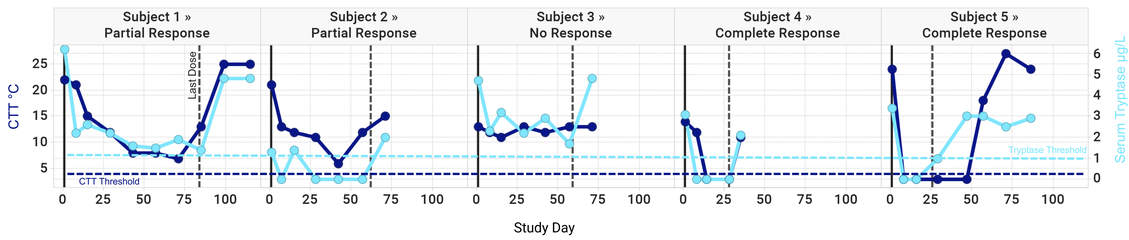
Two participants discontinued due to drug-induced liver injury AEs.

- Subject 2: 19 year-old Caucasian female with no significant past medical history
- Subject 3: 34 year-old Caucasian female with history of atopic dermatitis.
- Medical history was unremarkable for increased alcohol intake, change in prescribed or OTC medications or recent strenuous exercise
- Viral serology and ultrasound unremarkable, no change in synthetic function
- Both cases recorded as Drug Induced Liver Injury (DILI) AEs of moderate intensity and related to study drug
- Both DILI AEs fully resolved

- Hematology effects observed with mild reductions in neutrophils, leukocytes and reticulocytes
  - Considered an on-target effect given KIT expression on myeloid cells
  - Effect appears to stabilize after a few weeks followed by a trend toward improvement while on drug
  - Full return to baseline off drug
- Hemoglobin stable with no meaningful trends or clinically significant values noted

Note: Leukocyte and reticulocyte data not shown

Figure 5. Critical Temperature Threshold and Serum Tryptase by Subject



- Four of five participants treated achieved partial (n=2) or complete (n=2) Critical Temperature Threshold (CTT) responses despite early termination of dosing. Partial Response is defined as >4°C decrease in CTT from baseline, Complete Response is defined as CTT <= 4°C.
- Rapid and sustained reduction in serum tryptase was observed, with an 83.1% mean change from baseline as early as week one.
- Reductions in serum tryptase appear to correlate with clinical efficacy.

Note: Negative CTT results (complete response) are shown at 3 °C. Serum Tryptase values below lower limit of quantification are shown at 0 μg/L. Empty circles indicate results post treatment.

CONCLUSIONS

- The study was stopped early due to observed 'drug-induced liver injury' associated with clinically significant elevations in ALT and AST in 2 participants after 8 weeks of treatment with THB001 200 mg twice daily
  - No additional liver toxicity observed in any other participants
  - DILI AEs were rated moderate in severity and resolved at Weeks 17 and 25
- All other AEs were mild; No SAEs
- Expected on-target effects of KIT-inhibition were observed and were rated as mild.
  - Hematopoiesis: minor, reversible reductions in neutrophils, leukocytes and reticulocytes
  - Melanogenesis: reversible hair color changes in all subjects
- Pharmacokinetic concentrations were within the expected ranges at all visits (data not displayed)
- 4 of 5 participants achieved a complete (2) or partial (2) response in CTT after 2 weeks of dosing with corresponding reductions in serum tryptase
- These data suggest the potential for clinical efficacy with an oral, highly selective KIT inhibitor

DISCLOSURES

Brianne Leary, Ted Snyder, Steven P. Sweeney, Edward Conner: Salary: Third Harmonic Bio.; Stock and Options: Third Harmonic Bio.

Ismahaan Abdisalaam, Robert Rissmann: Funded Research: Third Harmonic Bio; Salary: CHDR

Martin Metz, Marcus Maurer: Funded Research: Third Harmonic Bio; Salary: Charité

Heike Röckmann: Salary: UMC Utrecht

Martijn van Doorn: Salary: Erasmus MC

Thomas Rustemeyer: Salary: Amsterdam UMC

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